Regulatory perspective on use of animal models to study therapeutics for filovirus infections

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NIAID Filovirus Workshop 9/12/07

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Goals: early discussion of development plans

- Mechanisms for facilitating therapeutics targeting life-threatening viral infections
- Potential uses of animal data, including “the Animal Rule” for drugs and biologic therapeutics
- Special provisions for enhanced interactions
- Comparison of science base with examples of vaccines and of bacterial biothreats
- Examples of unresolved scientific issues
- Getting interactions started

Mechanisms for facilitating therapeutics targeting life-threatening viral infections

(Note: discussion at this meeting is for general informational purposes and does not create regulatory policy or provide guidance for any specific development plan.)

Sequence of development and interactions

- Pre-IND consultations (often via written response)
  - Can be requested by government, academic, industry sponsor
  - Can include very preliminary data and development questions
- IND (Investigational New Drug) submission
  - After identification of compound, formulation by sponsor
  - Initial development plans and first US human protocol
  - Includes numerous types of early and advanced studies
- NDA or BLA (New Drug or Biologics License Application)
  - Approval/licensure as goal of product development
  - Adequate and well-controlled studies supporting effect/directions
  - Post-marketing studies to confirm effects, monitor safety etc.
- Facilitated interactions for promising drug, unmet need
  - Risk/benefit and scientific evidence balance always considered

Regulation and review of antiviral products

- Review process in Division of Antiviral Products
  - Office of Antimicrobial Products, FDA/CDER/OND
  - Reviews proposals and data for new antiviral drugs or new uses of existing drugs
  - Reviews drug products proposed as immunomodulators for viral infections
  - Also reviews antiviral therapeutic proteins and monoclonal antibodies under biologics regulations
- Collaborations and consultations with other divisions and centers as appropriate
  - Differing science base may alter expectations
  - Evaluations on case-by-case basis
  - Early and frequent communications encouraged

Potential uses of animal data

(including “the Animal Rule” for drugs and biologic therapeutics)

Relative roles of human and animal data

- Both will be relevant in varying combinations
- Consider extent of appropriately obtainable human data
  - Safety/PK, possible surrogate markers
  - Activity/efficacy for target or related viruses
  - Protocols for use/data collection in emergency
  - Benefit for populations at risk
- Animal data not limited to “Animal Rule”
  - Explore activity, dose, duration, treatment initiation times
  - Supporting information to maximize efficiency of human studies
- “How can combined data provide a comfort level that the product will work?” may sometimes be a better question than “Does the Animal Rule apply?”
- Pre-IND and early IND discussions can help to define

“Animal Rule”: considerations in antiviral drug/therapeutic development for filovirus infections

- 21 CFR 314.600 or 21 CFR 601.90
- Can human studies be done (feasible and ethical) –as pivotal or supporting information?
- Is there a suitable surrogate marker [21 CFR 314.500, “Subpart H”] or other mechanism for pursuing approval?
- Is pathophysiology well-understood in both animals and humans? [more concerns arise with “surrogate virus”]
- Are there well-characterized animal models that can be expected to predict human treatment responses?
- Are endpoints relevant?
- Can adequate data be generated to support dosing?
- Adequate plans for human studies if appropriate circumstances arise?

Special provisions for enhanced interactions

Balancing expedited access and scientific integrity of the development process

Mechanisms for expediting development and facilitating access

- Early pre-IND interactions are important for case-by-case evaluation of science base and development plans
  - Can include incremental interactions regarding animal studies
- “Fast Track” may be requested at early or late development stages
- Discussion of suitability for accelerated approval, animal rule approval, priority review
- If emergency arises when product has some supporting data short of NDA needs: IND protocols, Treatment IND, Emergency Use Authorization may be considered
- Pre-IND and IND submissions best route to prepare for EUA if appropriate circumstances arise
- Early discussion of human protocols in case of need

Recent developments in Expanded Access and Emergency Use Authorization

- Expanded Access, Investigational Drugs, Treatment Use
  - Federal Register 71(240):75147-68, 12/14/06, Proposed Rule
  - Considers population size, disease, risk/benefit evidence
  - Avoid interference with clinical trials needed for development
- Emergency Use Authorization of Medical Products
  - Final Guidance posted July 2007
  - Unapproved product/use, for life-threatening condition
  - Issued only in declared emergency, expires at its end
  - Does not replace studies to support approval
- Both consider status of disease, other drugs, risk/benefit
- Best preparatory approach is pre-IND or IND

Comparison of science base with examples of vaccines and of bacterial biothreats

Or, how much more isn’t known about filoviruses

Examples of factors to consider in comparing antivirals development and vaccine development

- Timing of intervention relative to virus exposure
- Timing of intervention relative to viral illness
- Expected clinical condition of host at time of intervention
- Understanding of markers that might predict clinical benefit
- Diversity of potential targets and mechanisms of action

Examples of factors to consider in comparing study of antivirals for filoviruses and study of antibiotics for anthrax and plague

- Understanding of host-pathogen interactions
- Host specificity of pathogen
- Diversity of pathogen species/strains and implications for pathogenesis
- Extent of prior human experience with drug (safety database, effect in similar diseases)
- Understanding of PK/PD parameters and clinical outcome correlates

Examples of unresolved scientific issues

Or, how much more isn’t known about filoviruses

Some examples of unresolved scientific issues recognized to date

- Differences in pathogenesis of different filovirus species and strains in different hosts
- Relative importance of viral replication and host responses at different stages of infection and illness
- Relative balance of beneficial and deleterious components of host responses at different stages of infection and illness
- Implications for antiviral interventions of all the above
  - Same intervention might have very different effects in different clinical settings
  - Correlation of a finding with outcome does not necessarily imply causality
  - Potential impact of magnitude, timing, and duration of intervention

And then there are the other unresolved scientific issues

-- the ones we don’t know enough to recognize yet

Getting interactions started

Frameworks for communicating early and often

Pre-IND consultation for proposed antivirals

- Request for pre-IND consultation can take place very early in development
- Sponsor can present initial data, hypotheses, questions for written feedback
- Provides venue for discussion of plans for animal studies, content of IND
- Can identify characteristics of product that may affect study plans (toxicity, route, mechanism)
- Begins incremental dialogue to continue after submission of IND

Some examples of relevant guidances, regulations, website information

- Guidances and draft guidances http://www.fda.gov/cder/guidance/index.htm and http://www.fda.gov/cber/guidelines.htm
  - Fast Track guidance
  - Virology studies guidance
  - Guidances on biotechnology products
  - EUA guidance
- Regulations
  - Subparts E, H, I, and Biologics equivalents
- Websites
  - Pre-IND interactions and contact information http://www.fda.gov/cder/ode4/preind/default.htm
  - Emerging viral infections page links to selected regulations and guidances http://www.fda.gov/cder/ode4/preind/emerging.htm